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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,177	TENGLER ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 December 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,6,8,10,11,19-21,25-41,46-48,50,51,60 and 61* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,6,8,10,11,19-21,25-41,46-48,50,51,60 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Formal Matters

Applicants' response and amendments to the claims, filed 12/15/2008, are acknowledged and entered. Claims 9, 12-18, 42-43, 49, and 52-58 have been cancelled by Applicant. Claims 1, 6, 8, 10-11, 19-21, 25-41, 46-48, 50-51, and 60-61 are pending and under examination.

Response to Arguments

Any previous rejections and/or objections to claims 9, 12-18, 42-43, 49, and 52-58 are **withdrawn** as being moot in light of Applicant's cancellation of the claims.

Claim Rejections - 35 USC § 112 – 2nd Paragraph – New Grounds of Rejection

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 6, 8, 10-11, 19, 40-41, 46-48, 50-51, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 40 recite the limitation "...wherein the one or more excipients..." in line 7 of claim 1 and line 8 of claim 40. There is insufficient antecedent basis for this limitation in the claims. Claims dependent from claims 1 and 40 are included in this rejection.

Claims 1, 6, 8, 10-11, 19, 40-41, 46-48, 50-51, and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 1 and 40 recite the limitation "...wherein the one or more excipients..." are selected from "excipients". It is not clear how an excipient can be selected from an excipient. Claims dependent from claims 1 and 40 are included in this rejection.

Claims 1, 6, 8, 10-11, 19-21, 25-41, 46-48, 50-51, and 60-61 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The instant claims are drawn to enveloped pharmaceutical compositions comprising phenylephrine for extended release and guaifenesin for immediate release. The compositions are recited to "release" specific amounts of phenylephrine and guaifenesin over specific time periods (*e.g.*, over 80% between 90 minutes and 6 hours). The claims are unclear because it is not apparent where such "release" occurs or how it is measured. For example, is it Applicant's intent that the "release" recited in the specification and claims is measured in water, 0.1 M HCl, or pH 7.5 simulated intestinal fluid *ex vivo*? Or, is it Applicant's intent that the "release" recited in the claims is measured *in vivo* by measuring blood levels of the agents after administration of the claimed composition to a mammal? The metes and bounds of the claims cannot be determined because the "release" of active agent from the claimed compositions will be different depending on where and how it is measured.

Claim Rejections - 35 USC § 112 – 1st Paragraph – New Grounds of Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 6, 8, 10-11, 19-21, 25-41, 46-48, 50-51, and 60-61 are again rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to an enveloped pharmaceutical composition defined in functional terms by the release characteristics of the first active agent and second active agent from the compositions (*e.g.*, "over 80% between 90 minutes and 6 hours").

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to generic compositions comprising a first and second active, *i.e.*, generic enveloped pharmaceutical compositions defined only by the release profiles of the actives.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

In the instant case, the claims are replete with functional language that fails to define of what the claimed pharmaceutical compositions are composed. Examples of such functional language include the following:

i) "...three of more layers of phenylephrine deposited on a sustained release bead for extended release of over 80% of the phenylephrine between 90 minutes and 6 hours"; and

ii) "an immediate release layer of guaifenesin disposed on the three or more layers of phenylephrine wherein over 80% of the guaifenesin is released within 60 minute".

In the above examples, there is no description of what excipients allow for the claimed release profile of the first active agent, of what the "sustained release bead" is composed, or what extended release excipients allow for the claimed release profile of phenylephrine. As such, the claims lack written description because the claimed pharmaceutical compositions are not adequately described in a manner that would indicate of what the compositions are composed.

The lack of written description of the instantly claimed compositions is further compounded by the fact that the compositions require specific release profiles of the first and second active agents. Accordingly, other than the specific formulations described in the examples (pages 23-25), Applicants have not described the enveloping materials, excipients, carriers, or extended release coatings, or the amounts of such components, that would result in the claimed first and second active agent release profiles.

Aside from the very limited examples provided in the specification, Applicants provide no direction as to (a) what excipients and extended release coatings out of all possible excipients and release coatings that exist in the art would have been reasonably expected to result in the claimed release profiles and (b) which of those excipients and extended release coatings actually *do* result in the claimed release profiles, without having to execute hit or miss testing practices in order to make such a determination.

The need for testing amongst varying species and amounts of excipients and release coatings to determine what combinations would result in the claimed release profiles demonstrates that Applicants were not in possession of the full scope of the compositions now presently claimed. "Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the Applicant was in possession of the claimed invention." Please see MPEP § 2163.

Despite the disclosure of numerous inactives, substrates, solubilizers, and other additives, *e.g.*, pages 17-23 of the specification, it remains that the claims recite solely functional pharmaceutical compositions containing phenylephrine and guaifenesin. With the exception of the specific formulations described in the examples, Applicants are imposing the burden of extensive testing upon the skilled artisan to identify those other excipients, carriers, inactives, and extended release coatings that may result in the claimed release profiles of the first and second active agents, but which Applicants have not identified and thus, were not in possession of, at the time of the present invention.

It has been held in patent law that a wish or plan for obtaining the invention as claimed does not provide adequate written description of a chemical invention. Rather, a precise definition, such as by structure, formula, chemical name or physical properties or a combination thereof, is required. Please reference, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004). In other words, though Applicants may have a plan for how to identify other excipients, carriers, inactives, and extended release coatings that may be amenable for use in the present invention, it remains that at the time of the invention, Applicants had not identified such excipients, carriers, in-actives, and extended release coatings, and, therefore, did not have written description of the full scope of the compositions now claimed.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 1115).

Applicant's arguments have been considered and are persuasive with regard to the description of "enveloped", but not with regard to the description of the claimed enveloped pharmaceutical compositions generally. Other than a broad disclosure of numerous possible excipients, coatings, and additional additives, the claimed enveloped pharmaceutical compositions having the claimed release profiles of active agents have not been described, other than by the specific formulations in the examples, which comprise 7.5% phenylephrine immediate release beads coated with pharmaceutical glaze. Even in the examples, the coated beads that provide the claimed release profiles are specifically described as 10.93 kg of phenylephrine added to beads using 4.32 kg of "pharmaceutical glaze" (SR mix #1), 7.15 kg of SR mix #1 and 4.96 kg of pharmaceutical glaze, 4.75 kg of SR mix #1 and 2.68 kg of pharmaceutical glaze (second load), 5.92 kg of SR mix #1 and 3.43 kg of pharmaceutical glaze (third load), and 7.78 kg of SR mix #1 and 4.56 kg of pharmaceutical glaze (fourth load). Thus, other than phenylephrine for extended release comprising 10.93 kg of phenylephrine added to beads using 4.32 kg of "pharmaceutical glaze" (SR mix #1), 7.15 kg of SR mix #1 and 4.96 kg of pharmaceutical glaze, 4.75 kg of SR mix #1 and 2.68 kg of pharmaceutical glaze (second load), 5.92 kg of SR mix #1 and 3.43 kg of pharmaceutical glaze (third load), and 7.78 kg of SR mix #1 and 4.56 kg of pharmaceutical glaze (fourth load), Applicants have not described the

claimed "extended release coatings" that provide the claimed release profiles. In fact, it is noted that the disclosed SR Mix #1, SR Mix #2, SR Mix #3, and SR Mix #4 do not result in the recited release of "over 80% phenylephrine between 90 minutes and 6 hours" (page 24, [0083]). The maximum dissolution was 59.3% in 6 hours (SR Mix #1). Even when SR Mix #1 was combined with immediate release guaifenesin, less than 80% phenylephrine was released in 6 hours until week 12, when 85.5% phenylephrine was released in 6 hours (page 25, [0086]).

Applicants further argue that the application provides a description of sufficient, relevant, identifying characteristics of the claimed compositions. However, other than by stating that the compositions have a first active for immediate release and a second active for extended release, Applicants have not described of what excipients, layers, coatings, etc. the claimed compositions are composed. Nowhere in the claims or specification do Applicants provide a specific example of the claimed enveloped compositions having the claimed release profiles, other than phenylephrine for extended release comprising 10.93 kg of phenylephrine added to beads using 4.32 kg of "pharmaceutical glaze" (SR mix #1), 7.15 kg of SR mix #1 and 4.96 kg of pharmaceutical glaze, 4.75 kg of SR mix #1 and 2.68 kg of pharmaceutical glaze (second load), 5.92 kg of SR mix #1 and 3.43 kg of pharmaceutical glaze (third load), and 7.78 kg of SR mix #1 and 4.56 kg of pharmaceutical glaze (fourth load). However, as discussed *supra*, the disclosed SR Mix #1, SR Mix #2, SR Mix #3, and SR Mix #4 do not result in the claimed release of "over 80% phenylephrine between 90 minutes and 6 hours" (page 24, [0083]). The maximum dissolution was 59.3% in 6 hours (SR Mix #1). Even when SR Mix #1 was combined with immediate release guaifenesin, less than 80% phenylephrine was released in 6 hours until week 12, when 85.5% phenylephrine was released in 6 hours (page 25, [0086]).

Accordingly, the claims lack adequate written description of the claimed enveloped pharmaceutical compositions because the claims do not recite of what the compositions are composed, other than that they contain phenylephrine for extended release and guaifenesin for immediate release.

Claims 1, 6, 8, 10-11, 19, 40-41, 46-48, 50-51, and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Amended claims 1 and 40 recite the limitation "PEG". There is no support in the originally filed disclosure for the recited "PEG", other than PEG-4000 (page 19, line 23 of Specification). Accordingly, amended claims 1 and 40 introduce new matter into the claims.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to a generic genus, *i.e.*, "PEG".

Lack of Ipsis Verbis Support

The present application is void of support for the newly claimed "PEG". At page 19, line 24, Applicant discloses that "PEG-4000" is a suitable additive in the disclosed compositions. Applicant does not generally disclose the claimed "PEG" as recited in the instant claims.

Lack of Implicit or Inherent Support

Section 2163 of the MPEP states: "While there is no *in haec verba* requirement, newly added claim limitation must be supported in the specification through express, implicit, or inherent disclosure".

As discussed *supra*, Applicant discloses that the specific excipient, PEG-4000, is a suitable additive in the disclosed compositions. Nowhere does Applicant disclose or

suggest that "PEG-4000" is intended to encompass other polyethylene glycols as broadly encompassed by the recited "PEG". In this regard, Applicant's disclosure is very specific that it is "PEG-4000", not PEG generally, that can be included in the disclosed compositions. As such, while Applicant discloses "PEG-4000", one would not conclude that Applicant intended the broadly recited "PEG".

Claims 1, 6, 8, 10-11, 19, 40-41, 46-48, 50-51, and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Amended claims 1 and 40 recite enveloped pharmaceutical compositions comprising three or more layers of phenylephrine deposited on sustained release beads and an immediate release layer of guaifenesin "disposed on the three or more layers of phenylephrine" (claim 1) or "in contact with the three or more layers of phenylephrine" (claim 40). There is no support in the originally filed disclosure for the recited compositions, which the Examiner is interpreting as single beads coated with phenylephrine and then coated with guaifenesin. Accordingly, amended claims 1 and 40 introduce new matter into the claims.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117).

Lack of Ipsis Verbis Support

The present application is void of support for the claimed enveloped compositions wherein beads are coated with three of more layers of phenylephrine and subsequently coated with a layer of guaifenesin. The instant specification discloses enveloped compositions containing a first active packed for immediate release and a second active packed for extended release in a capsule (page 4, [0014]). Applicants explicitly state that the first and second actives are on separate carriers (id. at line 19). Also see page 6, [0020] wherein Applicants disclose a first active in powder form and second active packed for extended release that are encapsulated.

Lack of Implicit or Inherent Support

Section 2163 of the MPEP states: "While there is no *in haec verba* requirement, newly added claim limitation must be supported in the specification through express, implicit, or inherent disclosure".

As discussed *supra*, Applicant discloses enveloped compositions comprising a first active for immediate release and a second active for extended release wherein the first and second actives are on separate carriers. Also see the Examples in the specification. Nowhere does Applicant disclose or suggest enveloped pharmaceutical compositions comprising three or more layers of phenylephrine deposited on sustained release beads and an immediate release layer of guaifenesin "disposed on the three or more layers of phenylephrine" (claim 1) or "in contact with the three or more layers of phenylephrine" (claim 40). In this regard, Applicants explicitly teach away from such compositions wherein they state, "It was found that when the beads were overcoated with immediate release guaifenesin the process was not only time consuming (since building up the bead with guaifenesin had adhesion problems), but also that overcoating of the guaifenesin on the phenylephrine slowed the release of the phenylephrine to an unacceptable level" (page 6, lines 21-24).

Claims 1, 6, 8, 10-11, 19, 40-41, 46-48, 50-51, and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a

way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. This is a written description rejection, rather than an enablement rejection under 35 U.S.C. 112, first paragraph. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, 1st "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

The claims are drawn to compositions in which one or more actives can be selected from "stearic acid *derivatives*".

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, states that Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention, for purposes of the written description inquiry, is whatever is now claimed (see page 1117). A review of the language of the claims indicates that these claims are drawn to generic genera, *i.e.*, generic stearic acid derivatives.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

A description of a genus may be achieved by means of a recitation of a representative number of species falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). In *Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412), the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The court indicated that, while applicants are not required to disclose every species encompassed by a genus, the description of the genus is achieved by the recitation of a representative number of species falling within the scope of the claimed genus. At section B(i), the court states,

"An adequate written description of a DNA ... requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention."

There is not a single example or specie of the claimed stearic acid derivatives that is within the scope of the claimed genus. In the absence of sufficient recitation of distinguishing characteristics, the specification does not provide adequate written description of the claimed genus, which is a generic genus, *i.e.*, generic "stearic acid derivatives". One of skill in the art would not recognize from the disclosure that the applicant was in possession of the genus. The specification does not clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed (see *Vas-Cath* at page 1116).

Claims 1, 6, 8, 10-11, 19, 40-41, 46-48, , 50-51, and 59 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The instant claims recite enveloped pharmaceutical compositions comprising three or more "layers" of phenylephrine deposited on a sustained release bead for extended release of over 80% of the phenylephrine between 90 minutes and 6 hours (claim 1) or release of over 80% of the phenylephrine between 1 hour and 6 hours (claim 40) and an immediate release layer of guaifenesin in contact with the three or more layers of phenylephrine.

To be enabling, the specification of the patent application must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated that:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance

> with respect to the direction in which experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 wherein, citing *Ex parte Forman*, 230 USPQ 546 (Bd. Apls. 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,

2) the amount of direction or guidance provided,

3) the presence or absence of working examples,

4) the nature of the invention,

5) the state of the prior art,

6) the relative skill of those in the art,

7) the predictability of the art, and

8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. *In re Fisher*, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the *Wands* factors are relevant to the instant fact situation for the following reasons:

1. <u>The nature of the invention, state and predictability of the art, and relative skill of those in the art</u>

The invention relates to enveloped pharmaceutical compositions comprising three or more "layers" of phenylephrine deposited on a sustained release bead for extended release of over 80% of the phenylephrine between 90 minutes and 6 hours (claim 1) or release of over 80% of the phenylephrine between 1 hour and 6 hours (claim 40) and an immediate release layer of guaifenesin in contact with the three or more layers of

[1] As pointed out by the court in *In re Angstadt*, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

phenylephrine. The claims do not recite of what such compositions are composed. As such, the claims are overly broad, encompassing any excipients, extended release layers, etc. in any amounts.

The relative skill of those in the art is high, generally that of an M.D. or Ph.D. with several years of experience.

That factor is outweighed, however, by the unpredictable nature of the art. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, at 24 (In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved.), *Nationwide Chemical Corporation, et al. v. Wright, et al.*, 192 USPQ 95 (one skilled in chemical and biological arts cannot always reasonably predict how different chemical compounds and elements might behave under varying circumstances), *Ex parte Sudilovsky* 21 USPQ2d 1702 (Appellant's invention concerns pharmaceutical activity. Because there is no evidence of record of analogous activity for similar compounds, the art is relatively unpredictable) *In re Wright* 27 USPQ2d 1510 (the physiological activity of RNA viruses was sufficiently unpredictable that success in developing specific avian recombinant virus vaccine was uncertain).

In the instant case, although extended release compositions and coatings and excipients for making such extended release compositions are known in the art, it is not predictable, *a priori*, what coatings or excipients will result in any given release profile of active agent. Further, extended release coatings and compositions can be formulated so as to provide "release" of active agent in different body compartments such as the mouth, stomach, or intestines. An extended release composition formulated to release active agent in the stomach (*i.e.*, acidic environment) would not be expected to result in release of active agent in the intestines (*i.e.*, basic environment), or *vice versa*. The claims and instant specification do not disclose where the claimed "release" of active agents is intended to occur.

It is well established in the art that different extended release coatings and excipients affect the extent to which an active agent is release. In fact, the same release coating or excipient provided in different amounts can also change the release profile of an active agent from an extended release composition. For example, see USP No. 5,576,022, which discloses controlled release tacrine drug delivery systems. In Figure 6, the dissolution rate of seven different formulations was evaluated in water. These seven formulations were composed of different coatings in different amounts. CR1 is an immediate release pellet coated with hydroxypropyl methylcellulose (6% w/w), polyethylene glycol (15% w/w), spray talc (1% w/w), and water (92% w/w). Extended release pellets CR3, CR4, CR5, CR8, CR9, and CR10 were formulated by coating core pellets with different excipients in differing amounts (see Formulations described at cols. 12 to 18). It is clear from Figure 6 that one cannot simply deposit a layer of an active agent on a bead or coat a bead containing the active agent with anything coating in any amount and reasonably predict the dissolution profile of the resulting composition.

2. The breadth of the claims

The claims are extremely broad insofar as they disclose enveloped pharmaceutical compositions defined in purely functional terms (*i.e.*, by the release profiles of the active agents). The claims do not recite of what the compositions are composed other than to state that they are composed of layers of phenylephrine deposited on a "sustained release bead" and further coated with a layer of guaifenesin.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for determining the particular extended release coatings and excipients necessary to formulate the claimed compositions having the claimed release profiles. The specification provides no guidance for determining coatings or excipients that will predictably result in release of active agents in the mouth *versus* the stomach *versus* the intestines. The direction concerning formulating the claimed compositions is found in the specification at pages 23-24, which

merely discloses a generic formulation process wherein 7.5% immediate release beads were transferred to a rotating pan and phenylephrine was added to the beads using pharmaceutical glaze. These beads, described by Applicants as "sustained release mix #1" (SR mix #1) (see amendment to the specification filed 9/5/2006 at [0081]) were subsequently coated with different amounts of pharmaceutical glaze to make sustained release phenylephrine beads (SR Mix #2, SR Mix #3, and SR Mix #4) (page 23, [0082]). However, when these sustained release beads were tested for dissolution of phenylephrine, none of them resulted in the claimed release of over 80% within 6 hours (page 24, [0083]). Further, Applicants do not disclose in what medium (water, acidic medium, basic medium) the beads were assayed in. Further still, these sustained release beads were not formulated according to the claimed application of "three of more layers of phenylephrine" on a "sustained release bead". Rather, immediate release phenylephrine beads "coated" with phenylephrine were subsequently coated with different amounts of pharmaceutical glaze. The sustained release phenylephrine beads were also not "coated" with an immediate release layer of guaifenesin but rather packed into a capsule with slugs of guaifenesin. As such, Applicants provide no working example of an enveloped pharmaceutical composition comprising "three or more layers of phenylephrine deposited on a sustained release bead" and coated with a layer of guaifenesin having the claimed release profiles.

The only specific formulations disclosed by Applicants are described at pages 26-27:

CAPSULE

First Active	Weight	Second Active	Weight
Guaifenesin DC	421 mg	Phenylephrine	15 mg
Talc	5 mg	Bead	44 mg
		Lacquer	6 mg
		Talc	5mg
		Calcium Stearate	5 mg

GELCAP

First Active	Weight	Second Active	Weight
Guaifenesin DC	421 mg	Phenylephrine	15 mg
Talc	0 mg	Bead	44 mg
		Lacquer	6 mg
		Talc	5mg
		Calcium Stearate	5 mg

SUPPOSITORY

First Active	Weight	Second Active	Weight
Guaifenesin DC	421 mg	Phenylephrine	5 mg
Talc	5 mg	Bead	15 mg
		Lacquer	2 mg
		Talc	1.5mg
		Calcium Stearate	1.5 mg
Stearic Acid	2 mg		
beeswax/glycerol	1-2 gr		

EFFERVESCENT TABLET

First EffervescentActive	Weight	Second Active Minicap		Weight
Guaifenesin DC	421 mg	Phenylephrine	15 mg	
Talc	5 mg	Bead	44 mg	
		Lacquer	6 mg	
		Talc	5 mg	
		Calcium Stearate	5 mg	
Monosodium citrate	10 mg			
Sodium bicarbonate	10 mg			

CAPLET

First Active	Weight	Second Active	Weight
Guaifenesin DC	421 mg	Phenylephrine	15 mg
Talc	3 mg	Bead	44 mg
		Lacquer	6mg
		Talc	5 mg
		Calcium Stearate	5 mg

It is not clear whether the second active in the above disclosed formulations have the release profiles of phenylephrine as recited in the claims.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art (as discussed *supra*) and in the absence of experimental evidence commensurate in scope with the claims, the skilled artisan would not accept the assertion that the instantly claimed enveloped pharmaceutical compositions could be predictably formulated as inferred in the claims and contemplated by the specification.

Genentech Inc. vs. Nova Nordisk states, "[A] patent is not a hunting license. It is not a reward for a search but a compensation for its successful conclusion and 'patent protection' is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" (42 USPQ 2d 1001, Fed. Circuit 1997).

In the instant case, Applicants have presented a general idea that one skilled in the art can readily formulate an enveloped pharmaceutical composition comprising phenylephrine for extended release of over 80% of the phenylephrine within 6 hours and guaifenesin for immediate release of over 80% guaifenesin within 60 minutes by simply applying three of more layers of phenylephrine to a sustained release bead and subsequently applying a layer of guaifenesin to the beads. However, the claims encompass compositions comprising any excipients, coatings, etc. in any amounts. Applicants formulated four phenylephrine bead types by simply coating 7.5% phenylephrine immediate release beads with phenylephrine and pharmaceutical glaze and subsequently coating the beads with differing amounts of "pharmaceutical glaze". When tested for dissolution in some unknown medium, none of the sustained release phenylephrine beads resulted in release of over 80% phenylephrine with 6 hours. In fact, only one sustained release bead (SR Mix #1) released over 11.0% phenylephrine in 6 hours (59.3%). As such, it is clear that it would take a tremendous amount of hit or miss experimentation in order to formulate the claimed compositions having the claimed release profiles given the limited guidance provided by Applicants. As noted *supra*, different excipients in different amounts have a tremendous, unpredictable affect on dissolution rates and the dissolution rate in water is not predictable of the dissolution rate in an acidic or basic environment such as the stomach or intestines.

Accordingly, the instant claims do not comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, since to practice the claimed invention a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success.

Claim Rejections - 35 USC § 103 – New Ground of Rejection

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 20-21, 25-29, 32-39, and 60-61 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Patel** (U.S. Patent No. 4,798,725; Issued Jan. 17, 1989) (newly cited) and **Davis *et al***. (US 2003/0049318 A1; Published Mar. 13, 2003) (prior art of record) in view of **Dang *et al***. (U.S. Patent No. 6,462,094; Issued Oct. 8, 2002).

Patel discloses a sustained release pharmaceutical capsule for oral administration comprising an active drug ingredient, polyvinylpyrrolidone and carboxyvinylpolymer (Abstract). It is also an object of the invention to provide a combination sustained release/rapid release pharmaceutical capsule for oral administration of an active agent (col. 2, lines 38-41).

Active drug ingredients, which may be used in the invention, include sympathominetic amines such as phenylephrine and expectorants such as guaifenesin (col. 6, lines 8-37). This teaching encompasses the active agents as recited in the instant claims. Amounts of active agent are recited at column 6, lines 55-60.

Combination sustained release/rapid release capsules are disclosed at column 8, line 35 to column 9, line 40 as well as in Example 8, such combined release capsules including for the rapid release of one active ingredient and a sustained release of a second active ingredient by incorporating different active drug ingredients in the first and second particulate mixtures described therein (col. 9, lines 27-33).

Release profiles are provided in the examples at columns 10-14. For example, in Example 1, the T_{90} (time required for 90% of active drug to be detected in dissolution media) in simulated intestinal fluid (SIF), pH 7.5, for a sustained release capsule comprising 51.1% by weight PVP was 4.0 hours. This clearly encompasses the extended release amounts and times as recited in claims 26-27 and 60-61. The reference thus provides one skilled in the art with the means and motivation to formulate a pharmaceutical composition, in the form of a capsule, comprising a rapid release formulation of one drug and a sustained release formulation of another drug.

Davis *et al.* disclose immediate and sustained release formulations of guaifenesin and additional drug ingredients, including a decongestant such as pseudoephedrine or phenylephrine (Abstract; page 4, ¶ [0045]). A specific formulation of immediate release guaifenesin and sustained release guaifenesin/pseudoephedrine is disclosed in Example 10. This formulation thus suggests and motivates the claimed immediate release expectorant (e.g., guaifenesin) and sustained release decongestant (e.g., phenylephrine) compositions and releases over 80% pseudoephedrine in 6 hours. The formulations of Davis relate to sustained release preparations in the form of capsules having beads or granules of both immediate release formulation and beads or granules of sustained release formulation, thus suggesting the limitations of the instant claims (page 2, ¶ [0019]). Davis *et al.* explicitly contemplate capsules (*i.e.* an enveloped composition) having a combination of "beads or granules of immediate release formulation and beads or

granules of sustained release formulation" (*i.e.* disposed in separate carriers) (page 4, ¶ [0043]). "Granules" (page 4, ¶ [0043]) of immediate release guaifenesin read on guaifenesin "in a powder form" as instantly claimed *(e.g.* claim 30). The formulations of the invention can also include other excipients (page 4, ¶ [0050]), thus teaching the limitations of claim 38. The reference thus motivates and suggests capsules containing both immediate release and sustained release formulations that can reasonably contain guaifenesin and phenylephrine.

Dang *et al*. is provided as further evidence that formulations comprising guaifenesin and phenylephrine were known in the art, thus providing motivation to formulate a composition according to Patel and Davis comprising these two specific drugs. Specifically, Dang *et al*. disclose that the novel formulation of phenylephrine tannate and guaifenesin produces a composition possessing sympathomimetic decongestant and expectorant properties superior to the use of either one of the compounds alone (col. 1, line 65 to col. 2, line 3).

The instantly claimed compositions would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention. Patel and Davis clearly teach, suggest, and motivate compositions comprising sustained release/rapid release pharmaceutical capsules for oral administration of one or more active agents, including compositions comprising immediate release guaifenesin and sustained release decongestant. Combination sustained release/rapid release capsules are explicitly suggested by the references, such combined release capsules including for the rapid release of one active ingredient and a sustained release of a second active ingredient by incorporating different active drug ingredients in the first and second particulate mixtures described therein. Davis *et al*. disclose immediate and sustained release formulations of guaifenesin and additional drug ingredients, including decongestants (*e.g.* pseudoephedrine and phenylephrine) (Abstract; page 4, ¶ [0045]). Said formulations relate to sustained release preparations in the form of capsules having beads or granules of both immediate release formulation and beads or granules of sustained release formulation, thus suggesting the limitations of the instant claims. Dang provides the motivation to formulate such a composition with guaifenesin and phenylephrine.

The instantly claimed release profiles are functional limitations, which could be readily determined through routine optimization of the compositions disclosed in Patel. For example, modifying the ratios of the sustained release layer of the Patel or Davis compositions would lead to different release profiles. Such optimization is not patentable over the prior art. The examples provided in Patel clearly demonstrate that modifying the amount of polyvinylpyrrolidone (PVP) affects the release rate of the sustained release capsules (Examples 1-5) and Davis et al. explicitly disclose a composition providing release of over 80% decongestant in 6 hours (Example 10).

Claims 30 and 31 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Patel** (U.S. Patent No. 4,798,725; Issued Jan. 17, 1989) and **Davis *et al***. (US 2003/0049318 A1; Published Mar. 13, 2003) in view of **Dang *et al***. (U.S. Patent No. 6,462,094; Issued Oct. 8, 2002) as applied to claims 20-21, 25-29, 32-39, and 60-61 above, and further in view of **Blume *et al.*** (U.S. Patent No. 6,372,252; Issued Apr. 16, 2002; Filed Apr. 18, 2000).

Patel, Davis, and Dang teach as applied supra and are herein applied in their entirety for the same teachings. Claims 30 and 31 differ from Patel, Davis, and Dang in that the references do not teach the claimed guaifenesin DC in powder form (claim 30) or an amount of 211 mg of 95% guaifenesin (claim 31).

However, Blume teaches a granulation of 95% guaifenesin DC (col. 8, lines 27-28) and immediate release tablets containing 211 mg guaifenesin DC (col. 16, Example 5).

As such, it would have been prima facie obvious to one ordinary skill in the art at the time the invention was made to use the guaifenesin DC in powder form in an amount of 211 mg of 95% guaifenesin as the immediate release active agent in the compositions of Patel and Davis because guaifenesin DC in powder form in an amount of 211 mg was known in the art to provide immediate release of guaifenesin.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 20-21, 25-39, and 60-61 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 and 19-37 of copending Application No. 11/010,944. Although the conflicting claims are not identical, they are not patentably distinct from each other because the copending application recites compositions comprising an expectorant for immediate release of over 90% within about 90 minutes and a decongestant for extended release. The expectorant is guaifenesin and the decongestant is phenylephrine in the claims of the '944 application and the same release profiles recited in the instant claims are recited in the '944 application claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614